6, line 24-page 7, line 11. Accordingly, the amendment adds no new matter.

In the parent application, U.S. Serial No. 07/586,543, Applicant filed a timely "Response to Final Office Action" under 37 C.F.R. §1.116 on June 29, 1993. The Examiner issued an Advisory Action on July 28, 1993, stating that applicant's response to the final rejection had been considered, but that the request for reconsideration did not overcome the rejection because "the references are directed to determining the 3-dimensional structure of the site of the function and designing drugs for it". Applicant cannot determine by this statement whether the Examiner is referring to the prior art references cited in the obviousness rejection under 35 U.S.C. §103 or the references submitted by applicant to overcome the enablement rejection under 35 U.S.C. §112, first paragraph. Therefore, applicant cannot determine which rejections have been maintained and which have been overcome. Clarification is respectfully requested.

Rejection Under 35 U.S.C. §103

In the Final Office Action mailed in the parent application on November 20, 1992, the Examiner rejected claims 1 and 3-19 under 35 U.S.C. §103 as obvious over Park et al., *Biochemistry, 28*: 2740-2746 (1989) in view of Endo et al., *J. Biol. Chem., 265*:

2216-2222 (1990) and Badger et al., *J. Mol. Biol., 207*: 163-174 (1989).

Park et al. disclose that substitution of the $G^3.U^{70}$ base pair in the acceptor helix of $tRNA^{Ala}$ with an $A^3.U^{70}$ base pair inhibits aminoacylation by alanyl-tRNA synthetase. However, Park et al. fail to appreciate that the $G^3.U^{70}$ site is within the minor groove and fail to teach, suggest or imply that compounds could be designed to bind and block a site in the minor groove of a target RNA in order to inhibit RNA function as claimed in the present application.

Endo et al. disclose the importance of the primary (nucleotide sequence) and secondary (stem, bulge, or loop) structural features necessary for α-sarcin to recognize and cleave rRNA, but fail to determine the tertiary (three-dimensional) structure, such as the major or minor groove, and its importance in RNA function.

Badger et al. disclose the three-dimensional, x-ray crystallographic analysis of **proteins** of drug-resistant human rhinovirus 14 and suggest the design of antiviral drugs that act by inhibiting these proteins. Badger et al. fail to disclose the tertiary structure of viral **RNA** and certainly do not suggest the design of drugs that would inhibit RNA function by binding in the minor groove.

Prior to applicant's discovery, those skilled in the art did not realize that the binding of compounds to nucleotides **within the minor groove** of targeted RNA could impair RNA function. Applicant, alone, was the first to discover and appreciate not only that sites in the minor groove of a functional RNA molecule could be critical for function (as evidenced by the subsequent publications of Musier-Forsyth et al., *Science, 253*: 784-786 (1991) and Musier-Forsyth et al., *Nature, 357*: 513-515 (1992)), but also, as taught in the present application, that it is advantageous to design and synthesize compounds having the ability to bind to those sites to inhibit target RNA function (see, e.g., page 6, line 28-page 7, line 18; page 39, lines 18-20 of the present application).

Rejection Under 35 U.S.C. §112, first paragraph

In the Final Office Action in the parent application, the Examiner objected to the specification and rejected claims 1 and 3-19 under 35 U.S.C. §112, first paragraph, on the basis that the claims were not enabled by the specification.

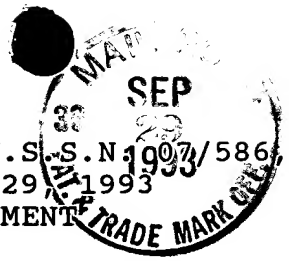
Claim 1 contains five steps for designing a drug to inhibit targeted RNA function, and claims 3-10 depend from Claim 1. The first step of claim 1 is to determine a sequence of the targeted RNA molecule critical to function; the second step is to determine the secondary structure of the region in which the

critical site is located; the third step is to determine the three-dimensional structure of the RNA, including the position of the critical site relative to the major and minor grooves; the fourth step is to determine the nucleotide sequences flanking the critical site, specific for the critical region and within the minor groove; and the fifth step is to synthesize compounds that will bind specifically to the critical site within the minor groove.

As described in the present application on page 9, lines 3-31, critical sequences of the targeted RNA are determined using methods well known to those skilled in the art such as substitutional mutation followed by a comparison of mutant versus wild type function or base substitution in tRNA followed by a determination of which amino acid is recognized by the altered tRNA. Specific examples of methods used to identify critical sites are given throughout the specification. For example, page 15, line 5 to page 18, line 12, describes determination of a critical site using anticodon substitution and transplantation assays. Examples 1, 2, 3 and 4 (pages 28-35 of the specification) also describe methods for critical site identification. The primary sequence of RNA molecules can be determined by a variety of routine nucleic acid sequencing methods. It is well known that knowledge of the primary sequence of an RNA molecule, enables those skilled in the art to readily

deduce secondary structural features of the molecule (such as a stem, bulge, loop, or clover leaf) formed as the result of intrastrand complementary hybridization. The tertiary (or three-dimensional) structure of the RNA molecule (such as the major and minor groove) can be determined using methods well known to those skilled in the art such as x-ray crystallography and cross-linking analysis. The sequences flanking the critical site are determined from the primary sequence. Compounds binding to the critical region in the minor groove are then designed using computer modelling programs as described in the specification on page 38, lines 9-15, and synthesized using methods well known to those skilled in the art as described in the specification on page 38, line 16 to page 39, line 30.

Therefore, one skilled in the art would have been able to perform each step recited in claim 1 without undue experimentation to design and synthesize novel compounds capable of inhibiting targeted RNA function.



Continuation of U.S.S.N. 07/586,534
Filed: September 29, 1993
PRELIMINARY AMENDMENT

Applicant respectfully requests that the Examiner enter the above preliminary amendment to claim 1 of this continuation application and pass the amended application to allowance.

Respectfully submitted,

Jamie L. Greene

Jamie L. Greene
Reg. No. 32,467

Date: September 29, 1993

KILPATRICK & CODY
1100 Peachtree Street, Suite 2800
Atlanta, Georgia 30309-4530
404/815-6608

CERTIFICATE OF MAILING UNDER 37 CFR § 1.10

I hereby certify that this paper and any documents referred to as attached therein are being deposited with the United States Postal Service on this date, September 29, 1993, in an envelope as "Express Mail Post Office to Addressee" service under 37 CFR § 1.10, Mailing Label Number TB458063122US addressed to Box FWC, Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Cecelia Dickerson